UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,890	06/21/2000	Milind Rajopadhye	DM-6999-A	7176

46339 7590 09/09/2005

BRISTOL - MYERS SQUIBB COMPANY
PO BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,890	RAJOPADHYE ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-87,90-93,96-98 and 100-110* is/are rejected.

7)☒ Claim(s) *88, 89, 94, 95 and 99* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 76-110 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 76-110 in the reply filed on 6/202005, is acknowledged. The traversal is on the ground(s) that "an indazole" in claim 76 and claim 101 represents only "carbon based- indazole" and that claim 106 should not be included in Group II. This is not found persuasive partly because the following reasons.

First of all, contrary to applicants' urging " an indazole" is not limited to carbon based moiety. The term "an indazole" is a generic term and can include various indazoles as evident form instant specification and original claim 1 and 2 wherein the "X" groups are independently permitted to be a combination of C and N.

Secondly, the present restriction is based on the first restriction and clearly adheres to the same format.

The requirement is still deemed proper.

However, inclusion of claim 107 is an error and upon further consideration, the restriction requirement of currently presented claims is withdrawn to apply the following.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 76-87, 90-93, 96-98 and 100-110 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected as it is dependent on rejected claim and shares the same indefiniteness.

1. Recitation of "an indazole" in claims 76 and 101, renders these claims and their dependent claims 77-87, 90-93, 96-98, 100 and 102-110 indefinite as it is not clear what is the structural make-up of the indazole is. As seen in specication and the originally presented generic claim and claim2, it appears to include any indazole whose structure is not defined.

2. Recitation of the term " an indazole nonpeptide" in claims 76 and 101, renders these claims and their dependent claims 77-87, 91-3, 96-98, 100 and 102-110 indefinite as it is not clear what is the structural make-up of the indazole nonpetide is. Specification has no definition of "an indazole nonpeptide" and it is not clear what is included in the nonpeptide portion and the peptide portion if any.

3. Claim 107 is indefinite for more than one reason. Recitation of " including" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

   Recitation of "stereoisomeric forms, thereof, or mixture of stereoisomeric forms thereof.... or prodrug forms thereof" renders the claim indefinite as it is not clear whether the composition should include all these forms in addition to the parent compound claimed. Note Markush choices should be in alternate form and in singular.

Recitation of "prodrug thereof" in claim 107 renders claim 107 indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable groups include such groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 107. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 107 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salt of the claimed compounds, does not reasonably provide enablement for making prodrug of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that

second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

There is no working example of a prodrug of a compound the formula (I). The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of

thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 76-87, 90-93, 96-98 and 100-110 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for composition of claims 88, 89, 94, 95 and 99 comprising a specific metallopharmaceutical with the recited functional language does not reasonably provide enablement for any or all metallopharmaceutical with varying metals, chelators, indazole nonpeptide with a functional language which include upregulation of angiogenesis generically embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

The instant composition claims 76-87, 90-93, 96-98,100-106 and 108-110 are drawn to " comprising: a metal, a chelator capable of chelating the metal, an indazole nonpeptide

targeting moiety covalently bound to the chelator, either directly or via an optional interposed linking group, wherein the targeting moiety binds to a receptor that is upregulated during angiogenesis; and at least one of a chemotherapeutic agent or a radiosensitizer agent." in general and the composition claim 107 relate to a genus of indazole nonpeptide of formula Ia or Ib, useful as chemotherapeutic agent or radiosensitizing agent for cancer chemotherapy in specific. The scope of the claims includes any or all metals, any or all chelators, any or linking groups, any or all indazoles with any or all receptor antagonism that relates to upregulation of angiogenesis including those yet to be discovered as due said mode of action for which there is no enabling disclosure. As recited, the scope of these claims includes large number metals, unknown number of chelators, millions and millions of indazole compounds and unknown of receptors for upregulation of angiogenesis. For lack of precise enabling disclosure, one trained in the art has to identify and make first millions and millions of indazoles as embraced in the term "an indazole" or formula I and Formula Ib and evaluate their interaction with large number of receptors whose numbers are undefined as embraced in the term " a receptor" and thus identify which of these compounds interact which of the unknown list of receptor. Having thus identified, by extensive experimentation, one trained in the art need to attach these compounds to chelator whose number and choices remains undefined with or without a linker group and reevaluate them with unknown list of receptor, select those which interact with a receptor that upregulate angiogenesis, select a metal from multitude of choices available , make all sort of chelated compounds and reevaluate their activity toward

the receptor to establish that they indeed upregulate angiogenesis and combine with a chemotherapeutic or radiosensitizer agent and establish that the composition indeed has the said functional property. Having done these extensive experimentation, one trained in the art has to redeem such a composition as applicants' composition which is by no means the criteria set forth in 112 first paragraph objective enablement requirement.

. The instant compounds are disclosed to be receptor vitronectin receptor antagonists and it is recited that the instant compounds are therefore useful as antagonists for any or all receptors diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action vitronectin antagonists that would be useful for all sorts of chemotherapy even when such a receptor is not involved and the compounds are antagonists of other receptors. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions and millions of compounds of claim 76 and claim 107 as well as large number of metals, unknown number of chelator, linker and receptors embraced by the terms a metal, an indazole nonpetide, chelator a receptor etc..

In addition, claim 76 is deemed as reach through claim wherein a mode of action or functional language is recited first and then compounds that relate to the mode of action is claimed. In the instant case because of the mode of action is a receptor antagonist with upregulation of angiogenesis inhibitor, the instant compounds are implied to be useful for chemotherapy.

No compound has ever been found to interact with any or all receptors generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of receptors and their ligands.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the Vitronectin receptor antagonist activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. Prior art search in the related area namely indazole compounds clearly shows that indazoles can have variety of uses with varying degree of interaction with macromolecules and it is not possible predict their action a priory. See for examples US 2005/010,457 which teaches indazole

as JNK inhibitors, US 2005/0101614, which teaches indazole useful as GABA antagonist and US 5,928,998 which teaches indazole as herbicides. (Note only few are cited to illustrate the point. Search in East database for indazole, class 548, subclasses .361.1, 362. 1, 362.5 & 364.5, show over 600 US Patents, most of these indazoles having interaction with receptors not involved in angiogenesis.)

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: " Composition comprising: a metal, a chelator capable of chelating the metal, an indazole nonpeptide targeting moiety covalently bound to the chelator, either directly or via an optional interposed linking group, and at least one of a chemotherapeutic agent or a radiosensitizer agent." that require receptor antagonist activity that upregulate angiogenesis

2) The state of the prior art: Prior art search in the area of indazole itself showed that activity of the said compound varies and is not limited instant vitronectin antagonistic activity. are unpredictable and are still exploratory. There was no evidence in the prior art that because a compound interact with a specific receptor such as vitronection would lead to interaction with any or all receptors and upregualte angiogenesis as embraced in the instant claims.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for upregulation of angiogenesis of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show a composition comprising any or all metals and any or chelators and any or all indazoles that interact with any or all receptors would lead upregulation angiogenesis and hence the desired use as chemotherapeutic agents and the state of the art as noted does not lend support for such a composition

6) The breadth of the claims: The instant claims embrace millions and millions of compounds various metals, chelators and linker groups. The breadth is too large.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general,

and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

Claims 88, 89, 94, 95 and 99 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

Venkataraman Balasubramanian

9/5/2005